TUBULYSINS AND PROTEIN-TUBULYSIN CONJUGATES

FIELD

[0001] Provided herein are novel tubulysins and protein conjugates thereof, and methods for treating a variety of diseases, disorders, and conditions including administering the tubulysins, and protein conjugates thereof.

BACKGROUND

[0002] While antibody-drug conjugates (ADCs) find increasing application in cancer treatment regimens, de novo or treatment-emergent resistance mechanisms could impair clinical benefit. Two resistance mechanisms that emerge under continuous ADC exposure in vitro include upregulation of transporters that confer multidrug resistance (MDR) and loss of cognate antigen expression. New technologies that circumvent these resistance mechanisms may serve to extend the utility of next generation ADCs.

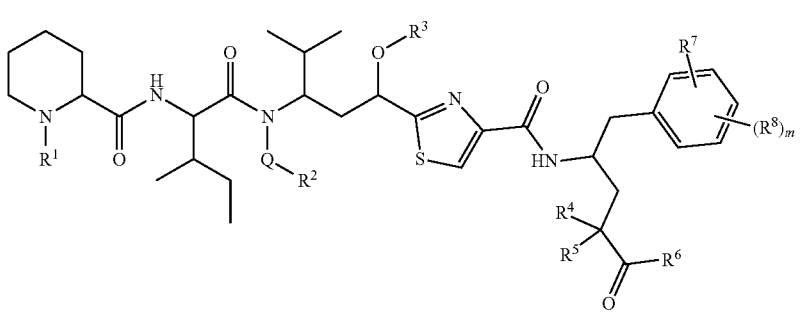
[0003] The tubulysins, first isolated from myxobacterial culture broth, are a group of extremely potent tubulin polymerization inhibitors that rapidly disintegrate the cytoskeleton of dividing cells and induce apoptosis. Tubulysins are comprised of N-methyl-D-pipecolinic acid (Mep), L-isoleucine (Ile), and tubuvaline (Tuv), which contains an unusual N,O-acetal and a secondary alcohol or acetoxy group. Tubulysins A, B, C, G, and I contain the C-terminal tubutyrosine (Tut) γ-amino acid, while D, E, F, and H instead have tubuphenylalanine (Tup) at this position (*Angew. Chem. Int. Ed. Engl.* 43, 4888-4892).

[0004] Tubulysins have emerged as promising anticancer leads due to their powerful activity in drug-resistant cells through a validated mechanism of action. The average cell growth inhibitory activity outperforms that of well-known epothilones, vinblastines, and taxols by 10-fold to more than 1000-fold, including activity against multi-drug resistant carcinoma (*Biochem. J* 2006, 396, 235-242; *Nat. Prod. Rep.* 2015, 32, 654-662). Tubulysins have extremely potent antiproliferative activity against cancer cells, including multidrug resistant KB-V1 cervix carcinoma cells. (*Angew. Chem. Int. Ed.* 2004, 43, 4888-4892; and *Biochemical Journal* 2006, 396, 235-242).

SUMMARY

[0005] Provided herein are compounds useful, for example, in anti-cancer and anti-angiogenesis treatments.

[0006] In one embodiment, provided are compounds having the structure of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is C_1-C_{10} alkyl;

R^3 is —C(O)C_1-C_5 alkyl, —C(O)N(H)C_1-C_{10} alkyl, or —(C_1-C_{10} alkylene)-$NR^{3a}R^{3b}$,

[0007] wherein R^{3a} and R^{3b} are independently in each instance, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^4 and R^5 are, independently in each instance, hydrogen or C_1-C_5 alkyl;

R^6 is —OH or —$NHNH_2$;

R^7 is, independently in each instance, hydrogen, —OH, halogen, or —$NR^{7a}R^{7b}$,

[0008] wherein R^{7a} and R^{7b} are independently in each instance, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, and amino acid residue, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^8 is, independently in each instance, hydrogen, deuterium, —NHR^9, or halogen,

[0009] wherein R^9 is hydrogen, —C_1-C_5 alkyl, or —C(O)C_1-C_5 alkyl; and

[0010] m is 1 or 2;

Q is —CH_2— or —O— wherein

[0011] when Q is —O—, then R^2 is C_1-C_{10} alkyl, C_1-C_{10} alkynyl, —C_1-C_{10} alkylene-(5-membered heteroaryl), —C_1-C_3 alkylene-Q^1-$(CH_2)_n$aryl, or C_1-C_3 hydroxyalkyl; or

[0012] when Q is —CH_2—, then R^2 is C_5-C_{10} alkyl, C_1-C_{10} alkynyl, —C_1-C_{10} alkylene-(5-membered heteroaryl), —C_1-C_3 alkylene-Q^1-$(CH_2)_n$aryl, or C_1-C_3 hydroxyalkyl; and

Q^1 is —CH_2— or —O—;

wherein said heteroaryl is unsubstituted or substituted with alkyl, aminoalkyl, hydroxylalkyl, carboxyalkyl, benzyl, or phenyl;

wherein said aryl is unsubstituted or substituted with nitro or amino; and

wherein n is an integer from 1 to 5.